

thyroidism, diabetes mellitus, cachexia, disease of the liver, febrile disease, or primary and secondary myopathies.

Besides the sexual incompetence on an organic basis in Case 3, a diagnosis of diabetes insipidus was made. In view of the fact that creatinuria occurs in association with diseases of three other endocrine glands (thyroid, pancreas, and male gonad), it seems quite possible that the disturbance of the pituitary gland may have exerted additional influence in the production of the creatinuria.

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A CLINICAL AND PATHOLOGICAL STUDY OF NEURITIS IN THE TROPICS, WITH SPECIAL REFERENCE TO BERIBERI.

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Introductory Note. This clinical and pathological study represents our crystallized opinions upon the principal problems connected with the subject, after prolonged residence in the tropics in teaching, research and practice.

No attempt is made to review the literature or to cover the practical field completely.

It is our aim to elucidate "Neuritis in the Tropics" rather than "Tropical Neuritis," and to clarify as much as may be this exceedingly difficult subject.

Of the problems of tropical pathology, that of neuritis is one of the most interesting, baffling and important. It is still very far from being solved.

The literature on the subject is enormous and much of it is of little value. Perhaps in no other field do we see so much uncontrolled, incomplete or unreliable work used as a basis for so many

varied and often unwarranted conclusions. On the other hand, splendid, careful research has been done both in the laboratory and clinical fields, and contributions are being made which tend to simplify the problem. In fact, in some of its most important phases solution is already in sight.

At the very beginning of our problem we encountered difficulties in classification. While we know that etiologically there is more than one disease in the group of the neurites, neither by a study of the clinical picture nor the pathology have we information which clearly distinguishes between some varieties of known etiologic difference, much less between those of unknown causes. Sometimes it even is exceedingly difficult to state that a given picture in reality is neuritis.

Nevertheless, the only sound classifications are those based upon etiologic grounds, and to do this we must at times accept hypotheses tentatively as facts or classify arbitrarily. The problem is more complex in the tropics than it is in temperate climates because of the great prevalence of the endemic neuritis, generally called beriberi.

We shall be guided in our discussion by the following outline:

ETIOLOGICAL CLASSIFICATION OF MULTIPLE NEURITIS

A. *Intrinsic Factors:*

Heredity (anatomic, physiologic and social status).

B. *Physical Agents:*

Traumatism and pressure.

Meteorologic and climatic conditions (altitude, atmospheric pressure, heat, cold, moisture, winds).

Occupation, electricity.

Environment in general.

C. *Chemical Poisons:*

Inorganic (arsenic, lead, etc.).

Organic (alcohol, etc.).

D. *Intoxications:*

Exogenous—food and other substances already poisonous when taken, toxins formed in various ways in the alimentary canal.

Endogenous (excluding toxins of known biologic agents):

1. Toxins formed within the body and due to derangement of metabolism, in nephritis, anemia, etc.
2. Internal secretion disturbances.

E. *Biologic Agents* (including their toxins):

Animal—syphilis, malaria, hookworm, schistosoma, trypanosoma, etc.

Vegetable—tuberculosis, typhoid, diphtheria, undulant fever, leprosy, etc.

F. *Metabolism Disturbances Due to Faulty Food Balance:*

Neuritis in pregnant and parturient women.

Neuritis in nursing infants.

Endemic tropical neuritis, beriberi.

Most of the etiologic factors shown in the table, and which are concerned in the production of neuritis in other countries, must be reckoned with in a study of the disease as it exists in the tropics. The most careful direct search for the etiology in each case of neuritis and a diagnosis only after the most exhaustive study and elimination is specially urgent in the tropics, and, if done, will give two very desirable results: It will change the present custom of diagnosing practically all cases of neuritis as beriberi, and it will result in simplifying the beriberi problem by harmonizing the results of investigation.

Intrinsic Factors. Conditions inherent in the patient, including hereditary influences and possible intrauterine diseases, must be important predisposing factors in at least certain classes of neuritis.

The report of the government committees for the investigation of infant mortality in the Philippine Islands records an average intrauterine death-rate of over 30 per cent. The causes of these deaths are in part at least unknown, and a predisposing influence to disease of the nervous system among those who do not die is generally recognized.

The anatomic, physiologic and social status as it has been evolved out of a poor heredity, disease and all but universal malnutrition might well be supposed to leave the nervous system particularly susceptible to neuritis as we know it leaves other parts of the body for other diseases. Indeed, histologists are frequently surprised in their study of supposedly normal histologic tropical material to find the nerves abnormal and even at times showing the picture of neuritis.

Neuritis Caused by Physical Agents. It is probable that physical agents are more important factors in the production of neuritis in the tropics than elsewhere. This may be due in part to special environment, and there are facts which indicate that neuritis may be produced in an Oriental by conditions which would rarely lead to such a result in temperate climates.

As an example, neuritis of the lower extremities is quite frequent during the latter months of pregnancy. In many instances the complication may be beriberi. Apart from this phase, which will be discussed under beriberi, there is a considerable number of these varieties that have little resemblance to beriberi. There are no cardiac symptoms or other evidences pointing to a serious condition. They appear to be due to pelvic pressure and to the water-logged edema of the dependent parts. This condition, noted but rarely in temperate climates, is quite prevalent in the tropics.

Neuritis from pressure by tumors, aneurysms and tight bands worn by certain tropical people is noted occasionally, and it sometimes follows the extensive traumatic wounds so frequently encountered in the land of the bolo and the kris.

Posture has been thought to be a factor in the preponderating prevalence of neuritis of the lower extremities over that of other parts of the body. Most Orientals rest in the squatting position instead of upon a chair, and they may remain comfortable in such position for hours at a time. Acosta-Sison considers this fact responsible for the very great prevalence of malpositions of the uterus among Filipino women.

Sudden changes from the lowlands to the cool high altitude hill stations is associated with the development of neuritis too often to be explained by coincidence.

Other meteorologic and climatic conditions influence the progress of neuritis, and the sudden changes so often seen in the tropics from hot and dry to cool and humid, although slight as compared with similar changes in colder countries, nevertheless produce most profound effects upon people and may not be disregarded in considering the onset of neuritis.

What in a general sense may be termed tropical environment exerts a powerful and constantly acting adverse influence upon the nervous system of all persons. Just what particular factor or factors in the environment are most to blame is not fully understood, but it is probable that it is the composite picture made up of heat, moisture, sudden change, mode of living, worries and fretting, and the squalor, ignorance, poverty, mixed languages and general unestheticness of the whole thing—all acting together—that racks the nervous system of the foreigner and influences the propagation of the weak, emotional, unstable, hysteric type so general among Orientals. It perhaps would be going too far to say that these conditions are the actual causes of neuritis, but that they so successfully prepare the way that otherwise innocuous agents may bring it about seems likely.

Neuritis Caused by Inorganic Chemical Poisons. The only known variety of particular importance in the tropics is arsenic neuritis, and the careful observer finds this quite frequently. At one time arsenic was considered to be a cause of beriberi. Arsenic is used extensively by many of the dark-skinned races as a medicine to be taken internally and in lotions and powders for the skin. Its skin-bleaching properties are widely known, and frequently enormous amounts are used to lighten the color of the skin, which is the vain ambition of every native woman.

Lead paints and lead work in general is not extensively applied in the Orient and lead neuritis rarely is seen.

Neuritis Caused by Organic Chemicals. Alcoholic neuritis is the most prevalent type in this group, just as it is in other countries.

It is generally stated that tropical people are not important consumers of alcohol. This oft-repeated statement is open to serious doubt. Imported and taxable alcohols for beverages average about three-eighths less per capita in the Philippine Islands, for example, than in the United States. However, in making comparisons it must be remembered that the average size of Orientals is only a little over two-thirds that of Americans, that their nervous systems are more sensitive and that the effects of alcohol upon any person is greater than it is in a cold country. Furthermore, the most prevalent alcohols consumed by the great mass of Orientals are not taxable and not therefore included in statistics. There are a considerable number of home-made preparations of alcohol, from the palm, sugar cane, etc., that are just as effective, probably more so, in producing neuritis as the imported varieties.

In any event, alcoholic neuritis is quite frequently seen in our large clinics among all classes, and in most instances a tentative diagnosis of beriberi is made. A supposedly typical case of beriberi was used in a clinic for senior medical students. The instructor felt humiliated when positive evidence was secured that the patient was a gin-drinker and had averaged nearly a quart of gin a day for several years.

Neuritis due to the other recognized organic chemicals is not frequent enough to be of importance. However, there is a great practically unexplained field among the unknown local herbs used as medicine. Practically all Orientals are extensive users of "herbs" as medicine. Most trees, flowers, weeds, as well as many fish, insects and minerals, are included in this group of cure-alls. Some of these substances are known to contain active poisons, and many others no doubt belong to the same group.

Neuritis Due to Intoxication. Toxins introduced in food or formed in and absorbed from the alimentary canal are a vastly more important subject in the tropics than elsewhere. That neuritis may be caused by such direct intoxication seems likely. The activities of the great variety of capsulated aneurotic bacteria constantly forming part of the tropical intestinal flora offers a promising field for investigation.

"Ptomain" poisonings are exceedingly common, and the enormous prevalence in the tropics of intestinal derangements due to infections and to the questionable quality of much of the food eaten by the poor makes it likely that this subject is more important in the etiology of neuritis than we now realize.

Endogenous toxins formed as products of disease or from deranged metabolism caused by disease assumes special importance in the tropical problem of neuritis. In addition to such diseases as diabetes, rheumatism and nephritis we have an unusual number of anemias, cachexias, fevers and other pathologic conditions of unknown cause which are not infrequently forerunners of neuritis.

The recognized excess of lymphoid tissues, forerunners of the hyperactivity of ductless glands and consequent instability of internal secretions, constitutes an enticing field for tropical investigation, and is looked upon with suspicion as an influence in the production of tropical neuritis.

Neuritis Caused by Biologic Agents. Animal parasites, such as those causing syphilis, yaws, malaria, trypanosomiasis and schistosomiasis in particular, acting either directly or through their toxins, are the exciting causes of a certain percentage of neuritis. Other animal parasites, including the various intestinal worms, exert a pronounced effect upon the nervous system, particularly in children, and it is probable that they at times may be considered the exciting cause of neuritis.

Bacteria and other vegetable parasites which cause tuberculosis, leprosy, pneumonia, typhoid, influenza, whooping-cough, undulant fever, and gonorrhea in particular, are recognized as the exciting causes of neuritis. In this role they may act directly, as in the case of the leprosy bacillus, or indirectly through their toxins, as shown for example in the diphtheria toxin.

The unknown causative agents of certain other diseases, as small-pox and dengue-like fevers, also must be considered among the causes of neuritis.

As in the well-known cause of typhoid neuritis the bacteria must not bear the entire blame for the neuritis, which in reality often is due to the action of the bacteria in the presence of a nutritional deficiency caused by insufficient or improper food.

Incidence. The various forms of neuritis discussed up to this point have a much higher incidence in the tropics than is generally recognized. Except in clinics and in hospitals there seems to be a remarkable tendency to diagnose all of them as beriberi without further investigation. During one period of about six months a careful study of patients admitted to our service with a previous diagnosis of beriberi showed over 50 per cent of them to belong in other groups.

The clinical varieties of acute, chronic and residual conditions seen in neuritis elsewhere are found among those in the tropics. The clinical picture otherwise, as well as the pathology, prognosis and treatment, do not differ sufficiently from similar conditions in temperate climates to warrant special attention here. Diagnosis is more difficult, much more difficult, and will be considered in the discussion on beriberi.

After we have studied a series of cases of neuritis in a tropical community by all the means at our command, and have classified them as far as possible into groups of known causes, there still remains a very large proportion unaccounted for, and these we will consider under the most used name of beriberi.

BERIBERI.

Synonyms—Definitions—General Remarks.

Predisposing Causes:

Inherited and prenatal factors (breeding, constitution, temperament, etc.).

Physical factors (climate, meteorology, geography, etc.).

Social factors (age, race, sex, poverty, etc.).

Public health factors (sanitation, overcrowding, prisons, etc.).

Personal hygiene and personal health factors.

Incidence, predisposition and immunity.

Exciting Causes:

Brief review of the various theories.

Discussion of the various theories.

As a group disease.

Summary of present knowledge, conclusions.

*Pathological Anatomy.**Symptomatology* (introductory remarks):

Clinical types: Acute, chronic, rudimentary, residual conditions.

Complications (diagnosis, prognosis).

Prevention (public health measures, personal measures).

Treatment.

Synonyms. Kakke, asjike, loempe, endemic multiple neuritis, panneuritis endemica and many, many others.

Definition. A chronic or less frequently acute disease or group of diseases caused in whole or in part by faulty food supply, assimilation or metabolism. It is characterized pathologically by a multiple neuritis selective in type for the pneumogastric, phrenic, anterior tibial and peroneal nerves, but extending to other nerves as well; expressed clinically by edema, pain, paresthesias and absence of reflexes, particularly in the lower extremities, palpitation and dilatation of the heart, epigastric distress and absence of fever. It is endemic in most Tropical and Oriental countries and finds its highest incidence among the ignorant and exceedingly poor.

General Remarks. Beriberi is one of three or four diseases which, taken together, always have stood as an insurmountable barrier against progress, civic, economic and social, throughout the great Tropical and Oriental world. It is a large factor in the physical imperfection, mental primitiveness, social degradation, economic squalor and sanitary backwardness of the population of these countries. The history of the disease is well told in Vedder's excellent monograph on the subject. It has been known and something of its ravages recognized in China, Japan and probably elsewhere almost since the beginning of the Christian era. Practically no Oriental, Tropical or far-eastern country ever is free from

it. It occurs sporadically, endemically and pandemically. Without being contagious or infectious, it rises and falls and passes in great waves over vast territories of hundreds of millions of inhabitants. Its association with ignorance, squalor and poverty is so close and intimate that its statistical diagram might be taken as an index of the intelligence and progress of a community.

Predisposition and Immunity. Certain races appear to have a natural immunity against the disease, and certain of the Tropical races seem to be especially susceptible to it. Newcomers into a beriberi zone, whether of foreign or native birth, seem to be less susceptible in certain instances, while in others similar change appears to increase the risk to the immigrants. It is probable, however, that all of these observations may be satisfactorily explained by other forces than predisposition and immunity. One or a number of attacks of the disease does not produce immunity, and it is likely that no such quality exists.

Etiology (Predisposing Causes), Prenatal Influence. We have not sufficient evidence to justify a positive statement that there is anything in inheritance or prenatal disease which predisposes to beriberi. However, the frequency of the condition in infants and other facts point to the existence of some such influence.

The frightful infant mortality in all tropical countries, due in large part to the poverty and squalor of the people and the consequent physical unfitness of mothers, and particularly the sacrifice of intrauterine life from similar causes, which constitutes over 30 per cent of the fetal death-rate in the Philippine Islands, strongly suggests that prenatal conditions are in part responsible for the high incidence of beriberi under certain conditions and among certain people.

Physical Conditions. Beriberi finds its highest incidence under certain physiographic conditions, climate and rainfall, and is largely confined within certain geographic limits.

Environment favorable to the spread of beriberi is that generally described as the East, the Orient or the Tropics. This does not necessarily mean climate, heat, geography, rainfall, customs of the people, activities, energies or any other one thing, but a conglomeration of these and many others which molds all classes who dwell in it to a something in common or destroys them. This environment is the home of beriberi, as it is of so many other diseases and abnormalities.

The disease is common in the entire Malay Archipelago, India, Burmah, Ceylon, China, Japan, the Philippine Islands, Dutch Indies, Korea, Siam, New Zealand, Australia, Africa, South Sea Islands, South America and on ships in various seas. In some countries it is limited to certain areas, and outbreaks are recorded in many parts of the world.

Seasonally, beriberi appears to be a wet-weather disease. In

endemic areas it is found at all times of the year, but in most places from which we have reliable statistics it reaches its highest incidence during and just after the rainy season. There are exceptions to this rule, and in some locations variation in rainfall is not sufficient to warrant emphasis on the wet season. In the Philippine Islands the incidence curve is highest toward the end and shortly after the rainy season, but the difference is not striking, and some of the past epidemics have continued through more than one season.

Other physical conditions which seem to be associated with the prevalence of beriberi are shown in its selection of lowland and river valleys, being less prevalent in high altitudes and in interior cities.

Social Conditions. The disease may occur at any age and in both sexes, but it is much more prevalent among young adult males and during early infancy. It is rare among very old people, and, except the infantile variety, it is less frequent during childhood. While all races are susceptible the dark-skinned tropical people are the greatest sufferers, and in given localities certain nationals seem more susceptible than others. Thus Bradden notes that while the native Malayan suffers but little, Chinese immigrants in the Straits and Malay Archipelago show a high incidence and a high mortality rate. In the Philippine Islands the native Filipinos are the greatest sufferers, the Japanese come next, and the disease is comparatively rare among the Chinese. Members of the white race rarely contract the disease.

Occupation. The disease is rare in all countries among merchants, artisans, professional men and in general among members of the social upper strata. It reaches its highest incidence among teamsters, farmers, rice-workers and others of the unskilled-labor classes.

Poverty. Beriberi is *par excellence* a disease of the poor, ignorant and superstitious, and is comparatively rare among any other class in any country. The poverty factor of greatest importance is that of quality and quantity of food supply. Poor people buy and eat almost without question what their local community markets supply, and this varies in volume, nutritional value and balance, always being deficient in proteins and fats.

Public Health Conditions. Beriberi subjects, regardless of race or residence, belong largely to the class who constantly infringe every sanitary requirement. They are mostly residents of the slums of the great Oriental and tropical cities, which means the worst that can be imagined for human beings. The worst areas are most frequently located on low shore land, with dirty, crooked, unpaved alleys for roadways, without any or with inadequate water supply or appropriate means for handling sewage and garbage. House construction is of the adobe stone without proper foundation or elevation, with dark, damp, poorly ventilated rooms, shared by human beings and animals alike; or, in certain other

localities, house construction is of bamboo or grass. Water is carried from a distance and stands in dirty barrels or earthenware pots; the local markets are dirty and the insect-covered and dust-covered food handled and examined freely by the different purchasers.

Overcrowding. Overcrowding is the rule in the slums of all Oriental cities. House-sleeping capacity is measured frequently by as many persons as may have pallet room on the floor, both sexes, children, sick and well, sleeping together indiscriminately in closed rooms. Only too frequently public buildings, such as barracks, prisons, theaters, amusement halls, etc., are not much of an improvement on the home conditions of these people, and overcrowding in such places is the rule in many communities. Millions of people live under conditions where there is no such thing as cleanliness, as the Occidental understands the word, and where there is no such thing as health, as he understands the term. These conditions, with variations to meet local custom, give beriberi its highest incidence and are responsible for the former hypothesis that it was a *place disease*. Existence under such circumstances may well be a predisposing factor to any disease, including beriberi.

Personal Health and Hygiene. Other diseases are not known to predispose to beriberi. Aside from its prevalence among pregnant and parturient women, it attacks persons otherwise apparently in normal health as frequently as it does weaklings. However, various diseases and depressing influences, such as the acute infections, mental exertion, emotion and excesses of all kinds, are considered by Scheube and others as predisposing factors.

Exciting Causes. As in many another disease for which a definite cause has not been determined, the theories concerning the etiology of beriberi are almost as numerous as its investigators. Each of these theories has been valuable insofar as it has led to accurate investigation of particular phases of the disease and the conditions surrounding its onset and occurrence. In this way, the list of possible causes has been narrowed down to relatively few. Thus far study of changes produced in the patient by the disease has furnished little that throws light on the true immediate causative factor, although predisposing influences have thus been detected. Rather a study of the external conditions surrounding the patient, and especially a study of the epidemiology, including diets, has been fruitful in furnishing satisfactory working hypotheses, at least concerning the cause of the disease, its prevention and its treatment.

While it probably is true that the exact determining cause of beriberi has not yet been absolutely proved, yet we are of the opinion that our present knowledge is sufficient to render some of the theories as to its etiology of more than historic interest. Ven-

turing upon this assumption, we will be satisfied with a simple classification of the various theories and will make particular mention of only those which have been of importance in leading us to our present state of knowledge and those which are associated with the names of investigators whose names in themselves entitle their theories to our respect.

THEORIES CONCERNING ETIOLOGY OF BERIBERI.

A. *Intoxication:*

1. Inorganic chemical.

- (a) Arsenic: Ross.
- (b) Carbon dioxide: Ashmead.
- (c) Oxalate: Trentlein, Maurer.

2. Organic.

(1) Vegetable.

- (a) Spoiled rice: Braddon, Fletcher, Breandat, Gelpke.
- (b) Ptomaines.
- (c) Other poisons.

(2) Animal.

- (a) Fish: Gelpke, Mura, Grimm.

3. Undetermined: Manson.

B. *Infection:*

1. (a) Bacterial (definite): Pekelharing and Winkler, Sangerfield, Durham, Rost, Van Elcke, Okato and Kokubo, Musso and Morelli, Taylor, Wright, Wheate.
- (b) Bacterial theory but not any recognized *one*: Manson, Castellani, Arnold, Baelz, MacGilchrist, Stanley, Daniels, Pearse, Lovering, Schubert, Balz, Legendre, Lovelace, Scheube, Shibayama, Marchoux, Travers.
2. Protozoan: Glogner and Heavley, Hewlett and de Koste, Fajardo.
3. Nematodes: Noc Kynsey.
4. Fungi: Rose.

C. *Deficiency in Diet:*

Phosphorus: Schaumann, Aron.

Nitrogen: Takaki.

Potassium: Fales (and green vegetables).

Proteins and fat: Van Leent.

Poorly balanced, monotonous and inefficient diet: Vordermann, Braddon, Fraser and Stanley, Eijkman, Grijns, Highet, Nocht, Woolley, Chamberlain and Vedder,¹ Strong and Crowell, Heiser, Kilbourne, Hunter and Koch, Holst, Frohlich, Herzog, Gimlette, De Haan, Little, Darling,¹ Funk,¹ Williams,¹ Gibson.¹

¹ Specific vitamine.

As indicated, beriberi occurs for the most part in tropical countries, and the classification given above indicates that practically all the theories that have been advanced recognize that the disease depends on the nature of ingested material. This is true whether the ingested material be harmful through insufficiency, through intrinsic poisonous properties or through forming favorable conditions for the development or growth of harmful material in the intestines. Almost all of the champions of the bacterial origin of the disease, among whom Wright holds a prominent place, consider the alimentary tract to be the portal of entry. Wright does consider wound infection a possibility and Manson doubts that it is a food infection.

Aside from those who have described definite microorganisms as the cause of the disease there are others who believe that bacteria, protozoa or fungi may produce changes in the food before consumption, and those who favor the idea that the food forms a favorable medium for the growth of organisms either before or after ingestion.

Concerning the theories which consider inorganic chemical poisons as etiologic factors in this disease, it may be said that very little evidence in their favor has been deduced; they do not furnish a satisfactory explanation of the clinical or pathologic phenomena of the disease, and they have met with no general acceptance among workers on this subject. The same may be said of the theory of ichthyotoxismus and lathyrism.

Infectious Theory. Among the workers favoring the infectious theory there may be said to be two classes:

First among these are the ones who claim to have isolated organisms to which they have assigned an etiologic role; these may be dismissed from consideration at the present time, as none of their work has been confirmed or generally accepted.

The second class is an important one and includes those who, from a study of the epidemiology, symptomatology and pathology of the disease, consider that it is best explained by an infectious theory without themselves indicating any special organism as the one at fault. Their reasoning is largely by analogy with known infectious diseases. In a long list this group includes the names of such distinguished workers as Manson, Scheube, Wright and others.

Manson believes that the disease is caused by the introduction by inhalation or otherwise of a toxin generated by some germ without the body. This germ, he believes, may be carried by man from place to place. He considers beriberi especially a place disease.

Scheube's reasons for considering beriberi an infectious disease may be briefly summarized by stating his emphasis on its occurrence in strong, well-nourished young persons, its geographic restrictions,

its seasonal occurrence, and on his belief that it cannot depend on deficient nutrition.

Wright drew attention to and emphasized the changes in the stomach and duodenum, and he maintained that these are the seat of growth of an organism which produces an extracellular diffusible toxin, and this causes the lesions and symptoms of the disease.

Those theories which ascribed an etiologic role to nematode parasites have never been given serious consideration. A protozoan cause has never been proved, although protozoa have been found by some to be associated with the disease.

Diet. From the earliest time a relation has been noted between diet and beriberi. In the search for the true cause almost every conceivable relation between diet and the disease has been investigated. Especially has its relation to the consumption of rice occupied an important place in the history. In turn, workers have considered the chemical constituents of the varieties of rice, the time and degree of its decortication, the time and manner of its curing and preparation for consumption, the way in which it is stored, the length of time it is stored, the changes occurring in it while stored, and the amount eaten.

The names of Eijkman, Vordermann, Grijms, Braddon, Fraser and Stanton, Heiser, Strong and Crowell, Highet, Chamberlain and Vedder and Funk and some Japanese workers should especially be associated with the growth of knowledge concerning the relation of diet to beriberi. (Omission of names from this list is not intended to belittle the value of an investigator's work, but the list obviously has grown too large to be given complete.)

Some of the ways in which diet has been conceived to be related to the disease are indicated above. The theory which now attracts most attention and seems most plausible is that which regards highly polished rice as an exclusive or almost exclusive article of diet to be deficient in a substance or substances necessary for metabolism. The first step toward the proof of this theory was to establish the fact that the consumption of decorticated rice was followed by beriberi. This has been proved experimentally in man by Fraser and Stanton and by Strong and Crowell. It has also been shown by others on larger scales, as by Braddon, by Vordermann and by Heiser in Bilibid Prison and in the Cullion Leper Colony, where substitution of partly decorticated rice for completely decorticated rice led to the practical disappearance of beriberi.

Animal experimentation also has been of great value in advancing our knowledge of this disease. Eijkman in Java noticed the development of polyneuritis gallinarum in fowls fed on decorticated rice, and this work was soon confirmed by Grijns and others. The similarity between polyneuritis gallinarum and human beri-

beri was noted, and much fruitless discussion has been waged concerning their identity. It is sufficient to consider the two conditions analogous and apply truths elicited from a study of the fowl disease to man with caution. In this way it has been found possible to further our knowledge concerning the cause, prevention and treatment of the disease. It has been shown that fowls fed on fully decorticated rice develop polyneuritis, whereas those fed on slightly decorticated rice do not. From this the idea arose that a neuritis-preventing principle is present in the husk of the rice. It has been found, especially by the United States Army Board for the study of tropical diseases as they exist in the Philippines, that extracts of this husk (so-called rice-polishings; in Tagalog *tiqui-tiqui*) if given with decorticated rice will prevent the onset of the disease or cure it when present in fowl. This extract has also been found of value in the treatment of human beriberi, especially in the infantile form. Attempts at further purification of the neuritis-preventing principle have been made by Funk, Vedder and Williams, Edie and his co-workers, and Susuki, Shimamura and Odake. These workers have obtained substances with different chemical formulæ, so that it cannot be considered that the essential principle has been identified. Funk has given the name "vitamine" to the hypothetic substance which constitutes the neuritis-preventing principle. This had previously been shown to be alcohol-soluble by Chamberlain and Vedder.

Other articles of diet available to the poor in beriberi zones have been analyzed and tested as to their content of neuritis-preventing principles, and with great and often surprising variations. Furthermore, the nature and importance of "vitamines" in diseases other than neuritis have developed rapidly, and new facts that may be of value in the study of beriberi are being accumulated in many places.

Pathology. The condition of the general nutrition of the beriberi patient varies with the stage of the disease and possibly with its type. In the early stage the general nutrition may be good, while in the protracted case marked emaciation may occur. Attention has been drawn to the fact that in the so-called "wet" type of the disease the anasarca may conceal a poor state of general nutrition. It must also be noted that a good general state of nutrition may not indicate well-nourished nervous tissues.

Edema. All of the tissues may show a marked edema, and this is manifest by subcutaneous edema which may be widespread, or, in the early stages, confined to the lower extremities, by ascites, hydrothorax, hydropericardium, meningeal and pulmonary edema. Numerous explanations have been offered for the edema. It appears early in the disease and obviously before any renal or cardiac insufficiency is demonstrable. It also occurs in cases in which the anemia is insufficient to account for it. Degenerations

in the *nervi vasorum* have been demonstrated as well as degenerate muscular and intimal changes in the vessels. It seems probable that the edema is to be accounted for by some pathologic change in the vessel walls.

Heart. Hydropericardium may be relatively greater than transudation into the serous sacs, or at times may not be present at all. Herzog found hydropericardium present in 66 per cent of 256 cases collected from the literature. Epicardial ecchymoses are almost always present. Enlargement of the heart is the rule. In the acute pernicious type this enlargement is due to dilatation, especially of the right chambers. In the more chronic cases hypertrophy also occurs and the hypertrophy of the right ventricle is characteristic. Left-side hypertrophy may also occur, but is much rarer. A groove can usually be seen at the apex between the two ventricles. The heart muscle shows parenchymatous degeneration and edema, and may show fatty change. Fragmentation of the muscle fibres and hyaline degeneration have also been described. Nagayo has seen hyaline and fatty degeneration involving the bundle of His. Scheube, Balz, Pekelharing and Winkler have described small myocarditic foci such as are found in diphtheria and other infectious diseases. Scheube has seen cellular infiltration in the subepicardial tissues and small hemorrhages in the heart muscle and beneath the endocardium. Explanation of the cardiac hypertrophy, and especially its usual restriction to the right ventricle, is difficult. Most arguments advanced in explanation in no way elucidate it. Matzuoka's theory appears to us the best, namely, that it is dependent upon the congestion-edema of the lungs. The origin of the pulmonary edema has already been referred to as due to changes in the pulmonary vessels. Degeneration of the intramural cardiac nerves also occurs.

Lungs. Transudation into the pleural sac occurs, but is usually not extensive. The lungs show congestion and edema, usually most marked in the lower lobes. This may be sufficient to lead to splenization. Emphysema of the apical portions and free anterior margin is not uncommon. Aspiration bronchopneumonia sometimes occurs.

Liver. Congestion of the liver forms a part of the general visceral congestion and may advance sufficiently to give the nutmeg appearance. Parenchymatous and fatty degeneration occur as sequels of the congestion. Nagayo has described an excess of glycogen in the liver.

Spleen. No characteristic changes occur in the spleen in beriberi other than those due to passive congestion. The markedly enlarged spleens which have been described in beriberi are undoubtedly due to other causes.

Kidneys. These organs show the effects of passive congestion and parenchymatous degeneration. Fatty degeneration also sometimes occurs. A glomerulonephritis has been described in beriberi by Miura, but it is a fact that the kidneys in this disease show relatively slight changes, and these changes do not account for the edema. Other symptoms of renal insufficiency, such as albuminuria, are not the rule in beriberi.

Stomach and Intestine. Wright drew attention to and emphasized the changes occurring in the stomach and intestine. He says: "The stomach and duodenum are toneless, dilated and empty. Their mucosa is deeply congested, rugæ and valvulæ are flattened and present numerous small hemorrhagic injections. Rings and patches of brilliant congestion occur and prove to be markedly dilated capillaries. They suggest sprinklings of red pepper. This congestion and ingestion may be found as low as the cecum; in a few instances I have found it in the ascending colon. As a rule it is most marked and occasionally wholly confined to the pylorus and duodenum. A thin pellicle of treacle-like mucous has occasionally to be stripped from the congested mucosa, but no true membrane is ever formed. Infrequently the congestion proceeds to hemorrhagic erosion of the gastroduodenal mucosa. The first chain of mesenteric glands is usually swollen. Microscopically the gastrointestinal mucosa exhibits all the signs of an acute inflammatory process." Here it is that he found his Gram-positive bacillus to which he ascribed an etiologic role. In his cases of beriberi residual paralysis he says, "The stomach and small gut are generally slightly dilated, but there is a complete absence of the gastroduodenitis seen in the acute stage of the disease."

In addition to the changes described by Wright, we have found frequently in the acute cases a very marked edema of the mucosa of the stomach and upper part of the small intestine. Intestinal parasites, to which an etiologic role has been assigned by some, have been no more frequent in our cases than in a similar class of patients suffering from other diseases.

Adrenals. Nagayo has described a progressive hypertrophy of the medulla of the adrenals in beriberi. In some of our cases a relative prominence of the adrenal medulla has been noted, but this has not been found as a constant feature.

Thymus. Nagayo has also noted enlargement of the thymus in beriberi. Funk and Douglas maintained that among the changes which take place in pigeons suffering from polyneuritis as a result of an exclusive white-rice diet a marked diminution in size occurs in the glands of internal secretion. His most marked change was in the disappearance of the thymus; macroscopically no thymus could be seen in any of the pigeons with polyneuritis. Following these observations a theory that a severe change in the glands of internal secretion occurs in beriberi has been proposed by Funk

on the *a priori* ground that the vitamins of the food have a close relationship to the glands of internal secretion. Williams and Crowell concluded on experimental evidence that there is no fundamental connection between beriberi and atrophy of the thymus, and that when the latter occurs in birds fed on polished rice, as it frequently does, it is due to some other cause. So in our autopsy records of adult beriberi humans it is found that the thymus gland is usually small. Crowell has already drawn attention to the occurrence of enlarged thymus in some cases of infantile beriberi and its association with status thymicolymphaticus.

Pancreas. No change in the pancreas has been described as characteristic of beriberi.

Lymphatic Tissue. Nagayo notes the enlargement of the lymphatic apparatus and classifies it as a progressive (restorative) change. He says that the changes in the lymphatic tissues may be due to a poison. The lymphatic tissues of the body have been especially noted by us in our autopsy work, and no change in them has been found in beriberi unless associated with other stigmata of status thymicolymphaticus. We see no evidence which points to any unusual incidence of status thymicolymphaticus in beriberi.

Muscles. Beriberi has been defined as a neuromuscular degeneration. Following, or coincident with, the nerve degeneration there occur fatty, hyaline and colloid degeneration of the skeletal muscles. The muscle fibers become thin, lose their striation, become homogeneous and fragmented. Cellular infiltration and hemorrhages between and into the muscle bundles have been described. Marked atrophy of the muscles follows, with replacement of the muscle fibers by fibrous connective tissue.

Nervous System. To Scheube and Balz belong the credit of demonstrating for the first time that the essential lesion in beriberi is a degeneration of the peripheral nerves. The degeneration may be present in the central nervous system, but is most prominent in the peripheral nerves. According to Scheube, sensory and motor nerves to the muscles are most affected in the dry or atrophic form of the disease, vasomotor nerves in the wet or hydropic form and the vagi in the acute pernicious types of the disease. The nerve endings in the muscles, as well as the nerve stems, are affected. Changes have been described in the vagi and phrenics, in the splanchnics and their visceral branches, in the solar and renal plexuses, in the nervi vasorum, in the cervical sympathetic ganglia, in the cutaneous nerves and in the nerves of the extremities. The changes occurring in the peripheral nerves do not seem to us different in type from those occurring as the result of various organic and inorganic poisons, such as in diphtheria and typhoid and in alcohol, arsenic and lead-poisonings.

According to Scheube the most severe changes are in the muscle branches of the nerves, and the main nerves show slighter changes.

In general, he believes the grade of degeneration corresponds with the paralytic symptoms, the most severe changes occurring in the chronic cases, while acute cases may even die before degenerative changes are demonstrable. It has been held by some that the process originates in the peripheral nerve endings and extends centripetally, but this requires demonstration.

The change that occurs in the nerve is first a degeneration of the myelin sheath with its conversion into a fat-like substance that stains black with osmic acid. Within the neurilemma are seen globules of this degenerated myelin which may distend the neurilemma and give a beaded appearance to the nerve. At other places these globules are smaller and the neurilemma is not filled. The globules may be vacuolated and foamy in appearance or a long area of the myelin sheath may appear uniformly black and wavy after osmic impregnation. The degeneration is accompanied by a fragmentation of the axis-cylinder, which in appropriately stained preparation may be seen in comma-shaped or S-shaped fragments within the masses of degenerated myelin. Eventually the neurilemma sheath may entirely collapse and it may show a multiplication of nuclei which is interpreted as an effort toward regeneration of the axis-cylinder. Degeneration fibers in a nerve may be very numerous, or only a few may be seen in the small part of the nerve usually submitted to examination, while the other fibers appear intact. Durck has demonstrated tyrolysis and vacuolation of the ganglia cells in the anterior horns of the spinal cord and in the spinal ganglia.

Degenerations have also been described in the fibers of the columns of Goll, Burdach and Clarke in the nuclei of the funiculus gracilis and funiculus cuneatus. According to Wright the cells of the bulbar nuclei and the nucleus ambiguus on both sides are swollen, with excentrically placed nuclei and a massing of the tigroid bodies.

Degenerative changes have also been demonstrated in the intrinsic ganglia of the heart, in the vagal nerve endings and in the nerve endings in other viscera.

Special attention has been drawn by Japanese authors to the degenerative changes in the nerves in the vessel walls. In the meninges congestion is the rule and small hemorrhages may occur.

Symptomatology. The clinical manifestations may be best understood by classifying them under four varieties:

1. Usual type.
2. Severe fulminant or pernicious type.
3. Chronic type and residual conditions.

Usual Type. The onset usually is somewhat insidious. The patient complains of a general feeling of discomfort or, as sometimes expressed, feels toxic. There is more or less epigastric distress which varies from a sense of fullness and indigestion to more

or less actual pain. The patient tires easily and there may be headache of a dull, heavy character. This prodromal stage may last from one to two or three days. Frequently the disease seems to be brought out during some slight indisposition, such as a "cold," diarrhea, slight fever or fatigue from prolonged exertion. In these circumstances there are no prodromal symptoms which may be positively charged to the neuritis. In any case the symptoms characteristic of the disease develop quite rapidly, so that the typical clinical picture is established within two or three days, although it may be delayed for a week. In the order of development the symptoms do not follow a fixed rule. Usually, heaviness, numbness and more or less pain develop in the legs. This is noticeable on walking, from which the patient quickly tires. Numbness and paresthesias develop first in the calf muscles, to be followed by pain on motion and tenderness on pressure. Edema, noticeable first as slight pitting over the lower tibia, progresses gradually over the legs and feet and later in other parts of the body, particularly the hands and face.

Usually the epigastric symptoms are considered to be indigestion, and, as a matter of fact, this frequently is the complaint which takes the patient to a physician.

As the disease progresses the leg pains become decided, particularly on motion or pressure; the joints feel as if they were out of control; the numbness may extend to the hands, arms and face; the edema becomes noticeable in the face and hands; a general sense of depression and oppression is complained of and the gait becomes characteristic of the disease. The altered gait is principally characteristic in that it is neither ataxic nor spastic, but more a combination of the two, and within a few days the patient is no longer able to walk or to stand without assistance.

The patellar reflexes at the very beginning frequently show a transient period of increased excitability, but they quickly become markedly diminished and finally lost entirely. The superficial reflexes usually remain normal.

In the fully developed disease the patient stays in a fixed position because motion increases the pain; the face and more or less rapid respiration indicate embarrassed circulation. The facies in general are those of an ill patient, the skin varying from normal to more or less cyanosis, the face, legs, feet, hands and frequently other parts of the body showing more or less edema; respiration and pulse are accelerated. There is epigastric distress, pains and tenderness in the legs and sometimes in the upper extremities. Numbness and paresthesias are unevenly distributed and more extensive than the pain areas.

The secretion of urine is diminished and there not infrequently is some looseness of the bowels. Nausea and even vomiting may be present.

Examination of a patient at this time shows tachycardia due to myocardial changes and influenced in some cases by more or less fluid in the pericardial sac. The rapid respiration may be due to embarrassed circulation, or there may be some fluid in the pleural cavities, and there may be a cough with considerable fluid expectoration.

There is tenderness over nerve areas, more marked in the calves, and usually pain is much increased on motion of the lower extremities. The patellar reflexes are absent. There is nothing significant to be found by examination of the urine or blood.

The patient may continue in this condition for days or weeks, with but slight change. In fatal cases the symptoms get worse, the pulse increases in rate, the edema extends, more fluid is found in the serous cavities and the patient finally succumbs to cardiac failure, less frequently to paralysis of respiration, or sometimes to acute pulmonary edema.

In patients who recover, the symptoms subside slowly, frequently but not invariably in reverse order to their appearance. As the circulation improves and the edema subsides the enormous muscle-wasting becomes apparent. Convalescence is exceedingly slow, lasting frequently for many months, and sometimes complete restoration of function never is attained.

There may be considerable variation in the clinical picture even in what we have termed the usual type. All of the symptoms may not be present in a given patient, and the order of their appearance may vary also. In one patient the epigastric symptoms may be the most pronounced and annoying, in another the cardiac symptoms may predominate, and there is frequent and marked variation in the extent and amount of the edema. In fact the edema may be so slight and temporary that the "dry" stage may be considered to be primary. Some authors consider that the dry form does develop primarily without there ever having been edema. However the matter is not considered one requiring lengthy discussion.

Severe, Fulminant or Pernicious Type. This type differs from the former chiefly in the intensity of the disease and the early and fatal heart failure. The onset usually is sudden. The whole cycle of the disease may be completed within one day, although the average duration is two to five days. It may develop out of a previously milder case.

This type of beriberi is a veritable plague, with very acute symptoms, a rapid course and practically always fatal. It rarely is encountered sporadically but occurs in prisons and in overcrowded places where the disease is epidemic. The nature of the symptoms and the order of their appearance frequently is much the same as in the usual type, but much intensified. The circulatory symptoms are the striking and characteristic features. They appear early and are the first and sometimes practically the only ones

present. At first there is tachycardia followed by increased respiratory rate, cyanosis, rapid heart failure and death. Edema of the lungs may constitute the terminal condition.

From first to last the clinical picture may not be distinguishable from that of acute progressive heart failure due to myocardial insufficiency from other causes. The expression is anxious, skin moist, eyes staring and pupils dilated, heaving chest motion and diffuse palpatory thrills.

Epigastric distress with vomiting is an early, severe and constant symptom. When the disease is a little less malignant and patients live more than two or three days the clinical picture may approach more nearly that given for the usual type. The edema has time to develop and the clearer intelligence allows a keener appreciation of pain and other subjective symptoms. The accumulation of fluid in the serous cavities is noticeable, the urine diminished, and there is thirst and loss of appetite.

Mild or Rudimentary Type. The onset is insidious. The earliest symptoms consist in a feeling of languor, a dull, stuffed sensation in the epigastrium, heaviness, numbness and some tingling about the calves. The sensations in the legs frequently are more noticeable in the night or early morning, particularly during the cooler season, when after hot days there is quite a decided chill in the early morning hours. Examination of a patient at this time will reveal slight but definite tenderness of the calves, slightly exaggerated but more generally definitely diminished patellar reflexes and possibly some acceleration of the heart-beat. In the majority of instances the patient will show slight but definite disturbance in the gait, consisting of hesitation in lifting the foot and an uncertainty or delicacy or deliberateness in placing it on the ground again.

One rarely sees this stage in hospital or private practice, but in the outpatient clinics for the poor it is encountered with great frequency. Unless the disease advances beyond this point there may be a question as to whether or not it really is beriberi. Most of these patients are from teamsters, laborers, rice-workers and others whose occupation keeps them outside, and they attribute the condition to getting wet suddenly while being exposed to the heat.

As the disease progresses the pains in the muscles of the legs, particularly the calf muscles, become more pronounced. These pains are spasmodic—cramps—and during the intervals between pains paresthesias are more or less constant. There is often a constant soreness of the muscles, and weakness of the legs is complained of after a few days or weeks of the disease. Other symptoms are dizziness, increased by exposure to the sun or by close application of any kind; slight epigastric distress and frequently some slight nausea. *Objectively* not much is found. The calf muscles

and often other muscles are tender on pressure and the patellar reflexes are sluggish and sometimes absent. Edema is slight or absent and examination of the heart may be negative. The blood, urine and feces do not show anything definite.

The disease lasts from a few weeks to months and even years unless treatment is instituted. Under rest in bed or confinement to the house, appropriate food and a simple bitter tonic recovery is rapid. Apparently one attack does not confer immunity, but rather seems to increase the patient's susceptibility. We have seen the same patient with as many as three attacks in one year.

During the protracted period of invalidism the patients hobble about, eke out an existence in various ways and alternate in "cures."

Muscular spasms and cramps of the legs with some paresthesia, noted more during cool nights, is not by any means confined to the Orientals. Many Occidentals who have resided in the tropics for years are sufferers from it. In many instances the exceedingly mild condition takes on other symptoms which are definite and leave no doubt of the diagnosis of a neuritis.

Chronicity and Residual Conditions. Except in the acute fulminant type the natural tendency of beriberi is toward chronicity. It is primarily a long-drawn out, slow-acting process, with acute exacerbations and tedious recovery, blending often into residual conditions which may be permanent and always disappear very slowly.

Regardless of the manner of the onset and the presence or absence of edema we have in the chronic beriberics a large problem. The extent of incapacity varies from those slightly crippled with leg cramps and tachycardia on exertion to completely helpless invalids, emaciated and miserable with pain.

After all activities of disease have subsided the residual paralysis, muscle atrophy and cardiac hypertrophy and dilatation remain for long periods of time, and it not infrequently happens that complete restoration of form and function never takes place.

Analysis of Symptoms. Gait. The gait is characteristic principally in that it differs from the various ataxias and spastic gaits of well-known diseases. It differs somewhat in accordance with the nerves involved, and consequently the corresponding varieties of muscle atrophy. True ataxia is never seen, but a spastic gait resembling that of spastic spinal paralysis may occur during convalescence.

Disturbances of Motor Function. All stages of muscular inefficiency are encountered, from numbness and sluggish action in mild cases to complete paralysis in the severe prolonged cases. There is selectiveness and variety in muscular involvement corresponding exactly to the distribution of affected nerves. In the order of frequency the muscles of the feet, legs, hands and arms are involved. Beyond various muscles of the face and body those

of most importance and serious consequence being the diaphragm and heart muscles. The sphincters are not involved. The electric reactions are similar to those found in peripheral neuritis due to other causes.

Vasomotor and Sensory Changes. Paresthesias of many types and varying form from complete anesthesia to the most intense hyperesthesia always form a part of the clinical picture. Those most prevalent are localized anesthetic areas corresponding to the anatomic areas most involved in the disease. The lips and tongue are paresthetic, frequently without signs of muscular insufficiency. The physical conditions of cold, moisture, pressure, etc., that affect paresthetic areas apply here. In interpreting phenomena of anesthesia and paresthesia it is well to remember that usually our patients are among the most ignorant natives of the tropics, who appear to be less responsive to our ordinary testing methods, and unless care is used errors are liable, particularly in interpreting anesthesia.

Vasomotor dilatation of the superficial vessels of the skin may lead to the most pronounced perspiration, and rarely an erythematous blush in affected areas may be seen among the lighter-skinned patients.

Alterations in Reflexes. The patellar reflex may be increased for a brief period at the onset of the disease. In all established cases it is either decidedly diminished or more frequently entirely absent. Altered patellar reflex usually is one of the earliest symptoms to appear and among the last to be restored to normal after recovery from the disease.

Circulatory Disturbances. Tachycardia in varying degrees is a constant symptom. In mild cases it may be scarcely noticeable on resting and only shows an exaggerated reaction from the mildest exercise. In more severe cases it becomes a prominent symptom, justly causing great anxiety to the patient, who can feel the increased rate and labored action of the heart. Frequently there is precordial pain. The heart symptoms are due to myocardial changes, with dilatation more marked on the right side but later involving both ventricles.

Edema and the collection of fluid in the serous cavities to a greater or less extent occurs in most cases of the disease at one time or another.

It is not unlikely that the transudation and exudation are dependent upon some more or less definite factor in the course of the disease as yet unknown. The frequent presence of dry atrophy as opposed to edema may be a striking symptom throughout the course of the disease. The more or less complete transfer from "wet" to "dry" varieties in the same patient is not easily explained, except by assuming an as yet unknown influence in the etiology of the disease.

The accumulation of fluid in the pericardium or pleural cavity may be sufficient in quantity to cause serious consequences. The amount in the abdomen and elsewhere is smaller, but there usually is some in all serous cavities, at least in acute cases of the disease. The edema usually appears first in the feet and legs, hands and arms, then the face, and later in severe cases one sees a striking picture of general anasarca. Pulmonary edema is not an unusual form of termination of the acute disease.

Fever is not a symptom of beriberi, and when present is due to some associated condition.

The systolic *blood-pressure* is generally lower in the tropics, both among natives and foreign residents, than it is in temperate climates. Even taking this fact into consideration the records seem to show that beriberi produces a lowering in the systolic pressure. This was true in the experimental cases of the disease studied by Strong and Crowell.

Blood examinations by the usual laboratory methods show nothing characteristic of beriberi. What departures from normal there are may be explained by associated conditions. A number of writers have called attention to a relative mononuclear increase of varying degrees, but Chamberlain and Vedder and others have shown that the relative increase in the lymphocytes is a pretty general condition in the tropics.

Alimentary System. Epigastric discomfort or distress is frequently an early symptom—sometimes the very earliest in the disease. These symptoms are probably due in part to more or less disturbances in the duodenum and in part to interference with digestion. They may be entirely absent. Nausea and vomiting may be distressing symptoms in fulminant cases and are fairly frequent in less serious forms. Diarrhea and other symptoms of intestinal disturbances are not important.

Urinary System. The most important symptoms are the variations in the quantity of urine excreted. Frequently in severe types the quantity is much decreased, and it may cease altogether before death. At times in the dropsical form there may be a very marked increase in the quantity of the urine, a change usually simultaneous with the reabsorption of fluid from the edematous areas. There are no characteristic changes found in the urine on routine examination.

Diagnosis. In endemic zones there is usually no particular difficulty in arriving at a diagnosis of multiple neuritis. Unfortunately only too often the diagnosis of neuritis is accepted as synonymous with beriberi. The differentiation between beriberi and multiple neuritis of other etiology is not easy to make by direct examination, and is only justified after a painstaking and thorough investigation into the etiology of each case.

Beriberi is most frequently confounded perhaps with alcoholic

neuritis. This mistake is made easy by the unfortunate statement so frequently seen that Orientals do not take alcohol. There is no greater fallacy in print. The poor people consume very poor qualities of cheap spirits, gin or beer, and in addition different localities have many different crude methods of preparing alcoholic drinks.

Differentiation from various other cropsies and edemas ordinarily is not difficult. However, it seems advisable to call attention to the mechanical difficulties encountered in examining the reflexes in patients already with much edema, particularly of the legs.

Prognosis. The mortality rates, as in all other pandemic and epidemic diseases, vary greatly as reported from different countries, as well as from different localities in the same country. The mild form rarely is fatal, but it often changes, and quickly, to a more severe one with higher mortality, and this potential danger must be recognized. The acute fulminant type is practically always fatal. Mortality in the usual form varies from 2 per cent to 60 per cent as given by different authors and representing statistics from different endemic zones.

Preventive Measures. Whether considered from a public health, social or medical standpoint the prevention of tropical neuritis is a large and urgent problem. More than half the population of the world live within the endemic zone and the disease must be eliminated before great permanent progress will be made in the development of many countries.

Beriberi is essentially a disease associated with ignorance, squalor and poverty. The home *par excellence* of these conditions, and therefore the home of beriberi, is in the tropical and subtropical belts, with its hundreds of millions of ignorant, superstitious, poverty-stricken people who live in tropical filth and lead a hand-to-mouth existence without thought or care for the morrow, and only too frequently where efforts at improvement are received apathetically or are resented.

The task of providing the essential remedies of better homes, better food and cleaner living is a disheartening one. Temporary improvement may be achieved in local areas by organized government and other charities, but this further pauperizes the people and is an impossible permanent solution on a large scale from an economic standpoint. Compulsory control over the lives and activities of the people has been employed in places. It is an effort of doubtful utility and one certainly not free from danger. Permanent results may be achieved only by instilling the attributes of thrift, energy, cleanliness and physical development into the people. To do this would include the expenditure of large sums of money; require a firm, non-political government and the constant directing influence of skilled advice over a period of several generations. The energetic, thrifty, clean-living citizen is at present

a tropical exotic, and the propagation of a population of this class is unlikely. Certain things, however, may be done, and the most important is to secure by the best and most practical means applicable to any given community such improvement in the food supply as is possible. This may be done, as in the Philippine Islands, by teaching gardening in the public schools and stimulating the cooking and use of good home-grown foods.

There is no doubt but what "undermilled" rice is a safer article of diet than that with all of the pericarp removed, and under circumstances where it is practically the sole available foodstuff for the poor, every possible effort to secure its use should be employed. Enforced use of whole rice may, of course, be employed by the military and in prisons and certain other institutions under such complete control that the inmates have little to say about what they shall do or eat, but compulsion should not be attempted among a people who have a voice in their own affairs. The Philippine experiment illustrates this point: Although red rice is not delectable to a rice lover, it might have been made popular, just as the Bureau of Education made the use of maize popular, except for the great and widespread resentment created by endorsing its exclusive use among soldiers, lepers and prisoners.

Nations holding colonial interests within the endemic zone of tropical neuritis can render no greater service to humanity than by studying their local problems and applying methods that will ensure the universal use of a better and more varied diet than exists in those countries at the present time.

Treatment. The treatment of beriberi is symptomatic and specific. The vast majority of patients are too poor to buy medicines, and when they do succeed it is at the sacrifice of food for themselves and perhaps their children. A clean bed in a light sanitary room and proper food will cure more of these patients than medicine, and it is less expensive. A glass of milk is a better "tonic" than all the drugs in the pharmacopeia.

Among the better-class patients the refined methods of symptomatic treatment may be instituted. The circulatory, urinary and digestive functions should be watched. Strychnin, digitalis, atropin and various other heart stimulants have been recommended to guard against or relieve existing circulatory or respiratory embarrassment. They are of doubtful value. Absolute quiet in bed with an ice-bag over the heart will do much to prevent the necessity of treating urgent heart symptoms. Squills, citrate of potash and other similar remedies are used to relieve the diminution in urine secretion, but are also of doubtful value. Small doses of concentrated solution of magnesium sulphate are indicated when a laxative is necessary.

Specific Remedies. Quite a variety of drugs have had from time to time more or less vogue as specifics. It may be safely stated than none of them has any such properties.

Due largely to the researches of Funk, Vedder, Chamberlain and many others during the last few years, decided progress has been made toward a specific treatment of the disease by the use of appropriate foods and particularly by the use of extract of rice polishings and other substances rich in "vitamines." Some of the reports of the results of this method of treatment have been overly enthusiastic, but definite progress has been made and a sound foundation for further investigation established.

The extremely grave and widespread infantile type of beriberi (taon and many other local names), as well as the multiple neuritis of pregnant and parturient women, constitutes one of the most interesting and baffling problems in tropical neuritis, which may have consideration in a subsequent article.

CLINICAL DIFFERENTIATION OF EPIDEMIC ENCEPHALITIS, ACUTE POLIOMYELITIS, BOTULISM AND CERTAIN FORMS OF FOOD AND DRUG POISONING.

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EPIDEMIC encephalitis, botulism, certain forms of acute poliomyelitis and cerebrospinal syphilis, wood-alcohol poisoning and poisoning by drugs, such as veronal and members of the belladonna group present in common involvement of the cranial nerves resulting frequently in considerable diagnostic difficulty. It is the purpose of this paper to present a comparison of the various points which may be used in differential diagnosis of these conditions.

Poliomyelitis (Acute Poliomyelitis, Polioencephalitis, Infantile Paralysis or Heine-Medin's Disease) was first described by Jörg in 1816, who noted the occurrence of a febrile disease followed by paralysis of the limbs and subsequent club-foot. It is hardly necessary at the present moment to review the contributions to the subject of Heine-Medin, Wickman, Peabody, Draper and Dochez, Flexner and Amoss, Webster, Rosenow and many others more than to say that the old conception of the disease as expressed in the term "infantile paralysis" has given way to the recognition of the fact that the disease is a general infection in which paralysis may or may not occur. It is characterized upon an average by an incubation period of variable duration, usually about a week, followed by a stage of prodromal symptoms which are at times slight and of a very transitory nature and easily overlooked, then an acute stage with paralytic manifestations and lastly a period of retrogression. The prodromal symptoms are of a very general nature and vary from epidemic to epidemic. They may be so